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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/586,744	06/02/2000	John Joseph Harrington	9584-0017-999	7865

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EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 08/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/586,744	HARRINGTON ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

APPLICANTS FILED A NOTICE OF APPEAL ON JUNE 2, 2006. IN VIEW OF THIS FINAL OFFICE ACTION, IT APPEARS THAT THE APPLICATION IS RIPE FOR APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES AT THIS TIME. THEREFORE, THE TIME FOR FILING OF AN APPEAL BRIEF IS RESET TO BEGIN WITH THE WITH THE MAILING OF THIS OFFICE ACTION.

Status

1)☒ Responsive to communication(s) filed on *02 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,21-35 and 51-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,21-35 and 51-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Final Rejection

1. Applicants' reply, filed 6.2.2006, to a part of the Non-final Office Action mailed December 5, 2005, and addressing only the following issues - (1) a SUPPLEMENTAL DECLARATION , FOR REISSUE PATENT APPLICATION (37 CFR 1.175); (2) a Notice of Appeal; and (3) a Request for Extension of Time Under 37 CFR § 1.136(a), is acknowledged.

According to the Applicants "The Supplemental Declaration, executed by the Applicants in counterpart, is responsive to the request by the Examiner (made in paragraph 7 of the Office Action), and obviates the rejection of Claims 1-6, 21-35 and 51-84 under 35 USC § 251 as being based upon a defective oath/declaration."

Applicants further argue that "Although the Office Action is non-final, certain claims have been twice rejected, making the filing of an appeal proper (37 CFR § 41.31(a))."

Based upon the above arguments Applicants conclude that Claims 1-6, 21-35 and 51-84 are believed to be in condition for allowance.

2. The reissue oath/declaration filed with this application is defective (see 37 CFR 1.175 and MPEP § 1414) because of the following: The reissue oath/declaration filed June 2, 2006 is not signed by all the inventors.

Claims 1-6, 21-35 and 51-84 are rejected as being based upon a defective reissue oath under 35 U.S.C. 251 as set forth above. See 37 CFR 1.175.

The nature of the defect(s) in the oath is set forth in the discussion above in this Office action.

3. ***New Matter***

Claims 21-35 & 51-84 are rejected under 35 U.S.C. 251 as being based upon new matter added to the patent for which reissue is sought.

Applicant argue that It is well settled that amendments that replace subject matter incorporated into an application by reference with the **actual text and figures** of the incorporated document do not constitute new matter See, e.g., M.P.E.P 2163.07 (b).

By Applicants own arguments, it is acknowledged that replacing subject matter incorporated into an application by reference with the **actual** text and figures of the incorporated document do not constitute new matter. Therefore incorporation of the actual text or figures from Harrington and Lieber, 1995, J. Biol. Chem. 270: 4503 would be proper. However, neither the issued patent (U.S.P. 5,874,283) nor the incorporated reference of Harrington and Lieber (1995), describe the 'method of detecting the presence of a predetermined target nucleic acid..' of claims 21-35 & 51-84. Applicants may point to the actual text of the referred article of Harrington and Lieber (1995) or the issued patent in overcoming this rejection. There is no support in the instant specification or the incorporated reference that identifies the actual text which would indicate that the invention of claims 21-35 & 51-84 was **conceived at the time of filing this application**. Further there is no basis for methods of cleaving, detecting or substrate cleavable by FEN-1 or a kit or a method of detecting presence of predetermined nucleotide sequence in a sample. - (Claims 21-35 & 51-84). It may also be noted that the incorporated reference shows cleaving of the DNA molecule (not RNA) therefore has no basis for polynucleotide cleavage - RNA is not cleaved by FEN-1 (Harrington and Lieber, 1995, see

page 1240, column 2, last 2 lines). Similarly there is no basis for polynucleotides or 3' polynucleotides in the claims, whether it is for method of cleavage or substrate cleavable by FEN-1 or kits or method of detecting presence of predetermined nucleotide sequence in a sample.

Effective incorporation by reference is lacking. Applicants must clearly point out where in specification (or issued patent) or in the properly incorporated reference such methods or complexes have a clear-cut basis, or the invention was conceived at the time of filing this application.

Applicants' Previous Arguments:

Applicants argue that as explained during the personal interview on April 27, 2004, the 'adjacent polynucleotide is the "3' polynucleotide probe" is clearly defined in the reissue application at col. 11.17-24. Applicants further argue that the recited 5', 3'-double flap structures are cleaved by FEN-1 polypeptides.

In response, a method of cleaving a 5', 3'-double flap structure by murine FEN-1 (95% purified) is demonstrated by Harrington and Lieber, 1995, J. Biol. Chem. 270 : 4503, a reference that has been incorporated into this reissue application. The "3' polynucleotide probe" is defined in the reissue application at col. 11.17-24. However, no clear-cut method steps for 'detecting the presence of a predetermined target nucleic acid' [claims 21-35 & 77-84]; or a 'a substrate cleavable by FEN-1 polypeptide' [previously claiming a 'hybridization complex instead] [claims 51-58]; or a 'kit for detecting a target nucleic acid' [claims 59-76], or a method of detecting presence of predetermined nucleotide sequence in a sample [claims 77-84] as claimed are described neither in the

instant specification of this reissue application or in the incorporated Harrington and Lieber (1995) reference.

Applicants argue that the disclosure as originally filed clearly discloses a method for detecting the presence of a 'predetermined target nucleic acid' and point to column 11, lines 14-16.

However, there is no support for 'cleaving the 5', 3' double flap structure with a FEN-1 polypeptide. Further, there is no support for 'a list of **substrates** cleavable by a FEN-1 polypeptide' [see for example, claim 51], or lack support for 'cleaving a 3', 5'-**double** flap cleavage substrate [see for example, claim 77]. No such substrates are described. There is no support in the Applicants' citation(s) for the language 'double flap structure.'

The new matter rejection is maintained for improper incorporation of the actual text from Harrington and Lieber, 1995, J. Biol. Chem. 270 : 4503 or the instant specification.

As pointed out above the incorporated reference shows cleaving of the DNA molecule (not RNA) therefore has no basis for polynucleotide cleavage - RNA is not cleaved by FEN-1. Applicants have not addressed this issue. If Applicants are assuming a species/genus issue, wherein a species 'DNA' is taught and 'RNA' being within the scope of a skilled artisan, the examiner would disagree, because it is the double flap DNA that is cleavable not the RNA. The new matter rejection is maintained for this reason as well.

4. ***Written Description***

Claims 21-35, 51-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a method of detecting the presence of target nucleic acid, a substrate cleavable by a FEN-1 polypeptide and a kit for detecting the presence of a target nucleic acid (claims 21-35, 51-84). The instant claims contain no limitations that define the structures of the endonuclease (or FEN-1 SEQ ID NO :) or describe the predetermined structures of the target nucleic acid, or the double flap FEN-1 substrate, used for cleaving a polynucleotide comprising the 3' and 5' regions or that used in the detection method or for hybridization complex and kit. The incorporated reference of Harrington and Lieber, 1995, J. Biol. Chem. 270 : 4503, shows cleavage of 3',5'-double flap structure using Murine FEN-1 only.

While the specification describes four species of purified FEN-1 polypeptides viz., human FEN-1 (SEQ ID NO : 1), murine FEN-1 (SEQ ID NO : 3), yeast FEN-1 (SEQ ID NO : 5) and the endonuclease activity of RAD2 : SEQ ID NO : 7; and crude extracts of calf thymus, rabbit reticulocytes, Chinese hamster fibroblasts and Drosophila embryos have also been shown to possess FEN-1 activity. Although these species though have been shown to have FEN-1 activity, 3',5'-double flap cleavage activity is only been demonstrated in FEN-1 from murine, which is not representative of the entire FEN-1 3',5'-double flap cleaving (or hybridizing) genus. No hybridization or cleavage conditions are described. Applicants have not sufficiently defined the conditions under which the hybridizations cleavage activity are to take place. Nucleic acid hybridization assays are extremely sensitive to the conditions in which they are performed. The buffer composition, pH, temperature, length of time, salt concentrations, quality and

source of template nucleic acid, are all variables which determine the reproducibility of a given hybridization experiment. Given the unpredictability of the art and the nature of hybridization experiments in general, it is not sufficient to merely cite hybridization without a clear and explicit recitation of the conditions associated with the hybridization. For example, the definition of stringency as it pertains to hybridization conditions is subject to interpretation and is different from laboratory to laboratory. Therefore, without a clear and explicit recitation of the conditions which were actually used by Applicants in isolating the claimed polynucleotides which hybridize to the disclosed sequences, the skilled artisan would not be able to practice the claimed invention and would not be reasonably apprised of the metes and bounds of the claimed invention. Without such guidance, the experimentation left to those skilled in the art is undue. Including in the claims the exact nature of the hybridization conditions used to isolate the claimed polynucleotides would aid in overcoming this portion of the rejection.

Thus there is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of the polynucleotide probes by any identifying structural characteristics or properties other than stating that they are capable hybridizing under cleavage conditions (see claim 21, for example) or 'specifically hybridize (or anneal) immediately contiguously' (see claim 51, 59, 77 or 84, for example) and for which no predictability of structure is apparent nor the hybridization or cleavage conditions described. Given this lack of additional representative species as encompassed by

the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Arguments :

Applicants argue that the instant application describe a representative number of species of endonucleases adequate to provide written description support for the genus. For example, the disclosure describes four species of FEN-1 polypeptides : human FEN-1 (SEQ ID NO : 1), murine FEN-1 (SEQ ID NO : 3), yeast FEN-1 (SEQ ID NO : 5) & SEQ ID NO: 7. Further species of FEN-1 isolated from nuclear extracts of calf thymus, rabbit reticulocytes, Chinese hamster fibroblast and Drosophila embryos are described. These species adequately represent the genus of suitable endonucleases.

Applicants arguments having been considered as per the amendment filed October 3, 2005, but not found persuasive because of the following reasons:

Although 4 purified FEN-1 sequences of SEQ ID Nos. 1, 3, 5 or 7 and **four crude or nuclear extracts [obviously with no structure]** have been shown to have FEN-1 activity, only murine FEN-1 (SEQ ID NO: 3) has been shown to cleave 3',5'-double flap structure of Figure 12. Further, Applicants have not shown or described how the single species is representative of the entire genus of FEN-1. The structures of four FEN-1 is known, which however, is insufficient to be representative of the entire genus, because neither their structures are known to bear close similarity among each other nor have the various FEN-1 been shown to cleave 3',5'-double flap structure [with the exception of murine FEN-1 of SEQ ID NO: 3]. In essence, a single species

(murine FEN-1) has been described to cleave the double flap structure of Figure 12, which is insufficient to be representative of the entire genus. Even if all the eight species of FEN-1 were known to cleave 3',5'-double flap structure, it would still be not representative of the entire genus, because, such a genus would still encompass FEN-1 from hitherto undescribed or undisclosed sources, and for which no predictability of structure is apparent.

Likewise in the instant case, claims drawn to a method of cleaving a 5'-polynucleotide by FEN-1 do not functionally or structurally define the double flap structure used as substrates in the method [nor are structures well known in the art prior to the instant filing], for being acted upon by the FEN-1 polypeptide, and that the determination of suitable substrates or double flap structures would require testing by trial and error many known or unknown double flap structures to ascertain those which would function in the manner required by the claims, and would involve undue burden upon those skilled in the art.

Therefore, Applicants' arguments citing *University of Rochester v. G.D. Searle & Co. Inc.*, [wherein - A method patent for treating the side effects of pain relievers is invalid for failing to adequately describe the compound used in the claimed method, the U.S. District Court for the Western District of New York rules. Granting a summary judgment motion, the court reasons that the written description requirement of 35 U.S.C. §112 ¶1 cannot be satisfied by merely providing the desired function of the compound without more detail on the compound's structure, chemical formula, chemical name, or physical properties. The court also stresses the applicability of the written description requirements to the compound used, even though the patent

consists of method claims rather than compound claims. *University of Rochester v. G.D. Searle & Co. Inc.* Page 427], do not have a bearing in the instant case in view of reasons discussed. Further, as may be seen, not all claims are 'method claims', and cannot be grouped together in arguing the Rochester decision.

In the instant case Applicants have failed to articulate in describing the assay conditions (hybridization or cleavage) or describe the double flap structure of Figure 12, the compound(s) in question. Similarly, Applicants' claimed method of detecting the presence of target nucleic acid (claims 21-35, 78-84), or a substrate cleavable by FEN-1 (claims 51-58), a kit for detecting the presence of a target nucleic acid (claims 59-76) and method of detection of the presence of a predetermined nucleotide sequence (including how cleavage of the double flap is determined?) (claims 77-84), remain undescribed for lack of description of any FEN-1 capability to cleave any double-flap structure(s) as well as lack of description of the "3',5'-double flap structure" itself.

Applicants argue that the written description rejection is not understood, and these claims clearly describe which regions of the probes hybridize or anneal to which portions of the target polynucleotide, thereby dictating the three-dimensional structure of the resultant substrate.

Applicant's point is well taken. However, as noted in the rejection the claims as presented clearly lack all the key features required together, such as, (1) structure, (2) function and (3) hybridizations/cleavage conditions for the assay/method, in order to meet the written description requirement. Therefore, the written description rejection in maintained.

5. No claim is allowed.

6. **APPLICANTS FILED A NOTICE OF APPEAL ON JUNE 2, 2006. IN VIEW OF THIS FINAL OFFICE ACTION, IT APPEARS THAT THE APPLICATION IS RIPE FOR APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES AT THIS TIME. THEREFORE, THE TIME FOR FILING OF AN APPEAL BRIEF IS RESET TO BEGIN WITH THE WITH THE MAILING OF THIS OFFICE ACTION.**

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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